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(71) Applicant *(for all designated States except US)*: CRODA CHEMICALS INTERNATIONAL LIMITED [GB/GB]; Cowick Hall, Snaith, Goole, East Yorkshire DN14 9AA (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: STEEL, Ian [GB/GB]; 60 Becketts Park Drive, Headingley, Leeds, West Yorkshire LS6 3PL (GB). POSTMES, Theo [NL/NL]; Biomedical Research Foundation Maastricht, St. Servaasklooster 22, NL–6211 TE Maastricht (NL). KITCHEN, Guy, Stanley, Hawksworth [GB/GB]; 6 Beech Grove, Eldwick, Bingley, West Yorkshire BD16 3EG (GB).

(74) Agents: LINN, S., Jonathan et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

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(54) Title: PRODUCT AND METHOD OF EXTRACTING SAME

(57) Abstract

A method of extracting n–hexacosanol (C_{26} aliphatic alcohol), either per se or as a n–hexacosanol–rich mixture of aliphatic alcohols, particularly as a n–hexacosanol–rich mixture of C_{20} to C_{32} aliphatic alcohols, comprising extracting the alcohol or alcohol mixture from lanolin alcohols. The lanolin alcohols may be derived from unrefined wool wax by hydrolisis. The use of a lanolin source for the extraction of such C_{26}–rich higher aliphatic alcohol mixtures provides a much more economical source of such alcohols, which are particularly useful for their biological activity.

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PRODUCT AND METHOD OF EXTRACTING SAME

FIELD OF THE INVENTION

This invention relates to a method for obtaining particular mixtures of long chain aliphatic alcohols, which mixtures are rich in one or more particular selected higher aliphatic alcohol species, in particular n-hexacosanol. More particularly, the invention relates to a method of extracting these higher aliphatic alcohol fractions and the selected one or more higher aliphatic alcohol species contained therein from a lanolin-based source.

BACKGROUND OF THE INVENTION AND PRIOR ART

Long chain aliphatic alcohols typically having carbon chain lengths in the range C_{20} to C_{35} are known to have interesting and useful biological activity. Typically mixtures of these higher aliphatic alcohols occur naturally, for example in certain vegetable waxes, and it is known that these desirable fractions of higher aliphatic alcohols can be extracted from such natural sources and used in the formulation of various therapeutic products.

Mixtures of aliphatic alcohols having carbon chain lengths ranging from about C_{20} to about C_{26} are known to be useful for promoting corneal healing following injury to the eye, e.g. after laser ablative surgery, such as is

disclosed in US-A-5214071 and US-A-5296514. Additionally, various members of the group C_{20} to C_{28} aliphatic alcohols are known to be useful for treatment of viral infections and inflammation of skin and membranes, as is disclosed in US-A-5534554 and EP-A-0738141. Furthermore, in EP-A-0654262 there is disclosed a pharmaceutical composition for treating gastric and duodenal ulcers which comprises a mixture of higher primary aliphatic alcohols in the carbon chain length range C_{24} to C_{34} consisting of: 1-tetracosanol 9-15%; 1-hexacosanol 12-18%; 1-octacosanol 13-20%; 1-triacontanol 20-30%; 1-dotriacontanol 13-21%; 1-tetratriacontanol 1.5-3.5%.

One particular long chain aliphatic alcohol typically found in the above disclosed mixtures and which is of particular interest is n-hexacosanol (otherwise known as ceryl alcohol, $C_{26}H_{53}OH$). This particular substance is also known to have a neurotrophic effect on cultured CNS neurons as well as brain cells *in vivo*. It has also been found to be effective in elongating macrophages and increasing their uptake of particles. See for instance the disclosures in the following references: FEBS Letters, Volume 213, No. 2, 406-410 (March 1987); and Journal of Neuroscience Research 29, 62-67 (1991). Typically n-hexacosanol is active at extremely low concentrations, e.g. 500nM.

With the aim of extracting this particularly useful material n-hexacosanol either per se or as a n-hexacosanol-rich mixture of other higher aliphatic alcohols such as

those already known and disclosed above, various efforts have been made to derive such mixtures from natural sources where they have been found to occur.

For example, in published International Patent Application WO94/07830 there is disclosed the isolation from raw or refined sugar cane wax of a mixture of higher primary aliphatic alcohols of 24 to 34 carbon atoms chain lengths, which mixture is disclosed as being useful for a range of specific pharmacological benefits, namely for use as cholesterol-lowering, anti-platelet, anti-thrombotic and/or anti-ischemic agents, as well as for the antagonism of drug-induced ulcers and the improvement of male sexual activity. As most broadly defined in this reference, the isolated higher primary aliphatic alcohol mixture isolatable from the sugar cane wax source has the following composition: 1-tetracosanol 0.5-5.0%; 1-hexacosanol 5.0-15.0%; 1-heptacosanol 0.5-5.0%; 1-octacosanol 50.0-80.0%; 1-nonacosanol 0.5-3.0%; 1-triacontanol 6.0-20.0%; 1-dotriacontanol 1.0-10.0%; 1-tetratriacontanol 0.0-2.5%.

Specifically, n-hexacosanol is known to occur in the plant Hygrophila Erecta, which grows in India and Vietnam. However, this source of n-hexacosanol is extremely expensive and therefore impractical as an economically viable commercial source of significant amounts of the material for use in the pharmaceutical industry.

It is an object of the present invention to provide for the extraction in practically useful and economically viable amounts, of n-hexacosanol, in particular as n-hexacosanol-rich mixtures of higher aliphatic alcohols, from a new natural source. In accordance with the present invention, this new source for these materials is lanolin alcohols or even lanolin per se.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect the invention provides a method of extracting n-hexacosanol, either per se or as a n-hexacosanol-rich mixture of aliphatic alcohols, comprising extracting the alcohol or alcohol mixture from lanolin alcohols by suitable means. Preferably the method of the invention is a method for extracting n-hexacosanol, either per se or as an n-hexacosanol-rich mixture of aliphatic alcohols, from lanolin, the method comprising subjecting lanolin to hydrolysis and extracting or concentrating the desired alcohol mixture from the resulting mixture of lanolin alcohols. Optionally the method further comprises concentrating or isolating n-hexacosanol from the resulting extracted alcohol mixture.

In a second aspect the invention provides n-hexacosanol, or a n-hexacosanol-rich mixture of aliphatic alcohols, as or when produced by the method of the first aspect of the invention.

In a third aspect the invention provides the use of

lanolin, lanolin derivatives or lanolin alcohols as a source of n-hexacosanol, the use comprising extracting n-hexacosanol, either per se or as a n-hexacosanol-rich mixture of aliphatic alcohols, by suitable means from lanolin alcohols or a source of lanolin alcohols.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Preferred features and embodiments of the present invention in its various aspects will now be described in detail, by way of example only.

In the accompanying drawings:

Figure 1 is a schematic diagram showing an exemplary apparatus for carrying out the extraction method described in Example 5 below; and

Figure 2 is a schematic diagram showing an exemplary extraction cell configuration for use in the apparatus of Figure 1.

The preferred lanolin material which is the source of the particular higher aliphatic alcohol(s) of interest in accordance with the invention is lanolin alcohols, which are obtainable from ordinary lanolin or wool wax by hydrolysis or partial hydrolysis (i.e. controlled saponification) and subsequent extraction, both of these steps being in accordance with well known and well

documented procedures known in the art.

The invention resides in using at least these lanolin alcohols as the source of the desired aliphatic alcohol mixture rich in n-hexacosanol, although it is still within the scope of the invention for the overall preparative method to include preliminary steps of obtaining lanolin alcohols from unrefined wool wax by hydrolysis followed by extraction. If ordinary lanolin is used as the basic lanolin source, then particularly preferred is lanolin purified to varying levels of removed exogenous factors, such as allergens and pesticides, for example the hypoallergenic lanolin product sold by Westbrook Lanolin Company under the registered trade mark MEDILAN.

It is furthermore possible still within the scope of the invention for one or more lanolin derivatives, e.g. lanolin oil or lanolin esters, to be used instead as the basic lanolin source, with one or more appropriate preliminary preparative stages included in the overall method in order to generate the required lanolin alcohols which are then used as the source for the particular desired aliphatic alcohol mixture rich in n-hexacosanol.

The technique by which the required mixture of higher aliphatic alcohols is extracted from the lanolin source in accordance with the invention is not particularly critical, and a variety of preparative methods and process steps may be used in accordance with well established chemical

synthetic procedures, e.g. gel-permeation chromatography, solvent extraction, molecular distillation, fractional crystallisation, or any combination of these. Gel-permeation chromatography is the particularly preferred method of extracting the desired aliphatic alcohol mixture from the lanolin source.

Precise practical details of the abovementioned procedures will be well known and already widely practised by persons skilled in the art in this or neighbouring chemical fields, so they will not be described further here.

In accordance with the invention, the n-hexacosanol-rich mixtures derived from lanolin alcohols will generally comprise n-hexacosanol in an amount of at least about 2%, preferably at least about 5%, more preferably at least about 10%, even more preferably at least about 12 or 13%, by weight of the C_{20}-C_{35} fraction (or more preferably and particularly, the C_{20}-C_{32} fraction) of the alcohol mixture.

According to these preferred embodiments of the invention the aforementioned C_{20}-C_{32} fraction may form a proportion of the overall extracted alcohol mixture, i.e. alcohol components below C_{20} and/or above C_{32} may be present or it may be isolated per se, i.e. with such C_{20} and/or C_{32} alcohol components being substantially absent.

It has been found that by using a lanolin material as

the source of the particular mixtures of higher aliphatic alcohols rich in n-hexacosanol in accordance with the invention, it is possible to prepare hitherto unattainable concentrated samples of n-hexacosanol at an economical level, which can then be used in the formulation of e.g. medicaments, which will usually be in the form of creams, gels, salves, patches, lotions, liquid sprays, aerosols, tablets, capsules or any other suitable physical form for use in the therapeutic treatment of one or more ailments or conditions exhibited by a mammalian host, in particular a human. Typical therapeutic applications of the higher aliphatic alcohol mixtures rich in n-hexacosanol produced in accordance with the method of the invention include those disclosed in the prior art references mentioned hereinabove.

The present invention will be illustrated in further detail by the following Examples, which are not to be construed as limiting the scope of the invention.

EXAMPLES

In the examples which follow samples were analysed using gas chromatography-mass spectrometry against high purity standards obtained from Sigma. A Hewlett Packard 5890 GC - Hewlett Packard 5970 MSD system was used, fitted with a 30m x 0.25mm DB-1 capillary column (J+W) and a 1m x 0.32mm de-activated fused silica pre-column fitted with a zero-dead-volume connector (SGE). Helium carrier gas at 30 psi pressure was used in addition to Hewlett Packard oxygen

and moisture gas filters.

Temperature program details: 190°C start - hold temperature with 2°C min^{-1} ramp to 270°C, holding for 30 minutes.

The mass spectrometer was run in scan mode for detecting ions in the molecular weight range 10 - 800 units. 6 ions were used to characterise each peak.

As a reference standard example, a sample of lanolin alcohols (ARGOWAX (trade mark) distilled, batch no WM 1757, Westbrook Lanolin Company) was analysed using the above procedure. The results, which give good agreement with literature values (Literature reference: The Lanolin Book, Edited by Udo Hoppe, Published by Beiersdorf AG, Hamburg, ISBN 3-931146-05-7) are set out in Table 1 below.

Table 1

	WM 1757	Literature reference
C20	nd	0.2
C21	nd	trace
C22	0.30	0.2
C23	nd	0.1
C24	0.63	0.8
C25	nd	0.1
C26	0.78	0.7
C27	nd	no mention

C28	nd	0.1
C30	nd	0.1
C32	nd	0.1
C35	nd	no mention

In the results tabulated in the examples which follow, where "nd" is given this indicates a degree of uncertainty such that neither the identity of the species in question nor the amount of it present could be determined with any accuracy.

In the tables all values are % by weight of the total C_{20} to C_{32} fraction, unless otherwise stated.

Examples 1 to 4

In these examples gel permeation chromatography (GPC) was used as the extraction method.

Example 1

In order to illustrate the usefulness of lanolin as a practical source of n-hexacosanol, a sample of New Zealand-origin unrefined wool wax was converted into lanolin alcohols by hydrolysis and subsequent extraction, using standard techniques well known in the art.

The sample of lanolin alcohols prepared as above was separated into fractions using gel-permeation chromatography in order to generate a mixture of higher aliphatic alcohols containing predominantly C_{20} to C_{32}

aliphatic alcohols and being especially rich in n-hexacosanol. The experimental details were as follows:

The GPC column used was a 60cm x 2.5cm column containing 100g of Bio-beads SX3, with the eluent being a 50:50 (v/v) mixture of n-hexane and CH_2Cl_2. The lanolin alcohol sample was made up as a solution in the eluent mixture at a concentration of 2.5g of the lanolin alcohols in 25mls of solution. 7.5ml of this solution was loaded onto the column, with a flow rate of 5ml/min. Detection of material exiting the column was carried out using UV detection at 254nm. Sample collection started after an initial elution period of 20 minutes and thereafter 10 fractions were collected over a 40 minute period. Each of these fractions was subsequently analysed by gas chromatography and gas chromatography-mass spectrometry.

The third fraction which was collected was found to contain approximately 4.36% by weight n-hexacosanol. The complete results are shown in Table 2 below.

Table 2

Fraction	1	2	3	4	5	6	7	8	9	10
wt/mg	76	486	1570	1623	2686	1790	37	21	9	0
C20		nd	nd	nd	nd	nd		nd		
C21		nd	nd	nd	nd	nd		nd		
C22		nd	1.7	nd	nd	nd		nd		
C23		nd	nd	nd	nd	nd		nd		
C24		4.12	5.69	nd	nd	nd		nd		

C25		nd	nd	nd	nd	nd		nd		
C26		7.57	4.36	nd	nd	nd		nd		
C27		nd	nd	nd	nd	nd		nd		
C28		3.89	nd	nd	nd	nd		nd		
C30		2.57	nd	nd	nd	nd		nd		
C32		nd	nd	nd	nd	nd		nd		
C35		nd	nd	nd	nd	nd		nd		

Example 2

Fraction 3 (1570 mg) from Example 1 was re-fractionated by GPC on the same column and under the same conditions as described in Example 1 above, except that the flow rate was reduced to 2 ml min^{-1} and sample collection was delayed until 48 minutes after initial elution. The results are set out in Table 3 below.

Table 3

Fraction	1	2	3	4	5	6	7	8	9	10
wt/mg	4	5	5	9	31	67	261	44	19	7
C20	nd	nd	nd	0.58	nd	nd	0.55	1.63	nd	nd
C21	nd	nd	nd	0.40	nd	1.27	0.06	12.42?	nd	nd
C22	0.25	0.22	0.09	nd	nd	1.07	0.79	1.13	nd	nd
C23	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
C24	0.39	0.29	0.15	0.19	1.16	7.25	2.29	0.56	nd	nd
C25	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
C26	0.35	0.22	0.15	0.82	4.85	23.49	1.03	nd	nd	nd
C27	nd	nd	nd	1.05	0.31	11.58?	1.56?	nd	nd	nd
C28	0.33	0.16	0.28	0.85	2.85	1.78	nd	nd	nd	nd
C30	nd	nd	nd	1.47	1.15	0.23	nd	nd	nd	nd
C32	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
C35	nd	nd	nd	2.20	nd	nd	nd	nd	nd	nd

? indicates mixed peak

Example 3

Lanolin alcohols (ARGOWAX (trade mark) distilled, batch no. WM 1757, Westbrook Lanolin Company) were fractionated using the same procedure as in Example 2 above to give 10 fractions. Fraction 6 contained 25.17% by weight n-hexacosanol (C_{26} alcohol). Further fractionation of Fraction 6 yielded a fraction containing 44.51% by weight n-hexacosanol.

Example 4

The procedure of Example 1 was repeated, except that the gel permeation column used was a pre-packed Phenomenex Phenogel column (300mm x 21.2mm packed with 5μm styrene-divinyl benzene GPC media) in 50:50 (v/v) mixture of n-hexane and CH_2Cl_2 running at 2 ml min^{-1}. Detection of material exiting the column was again carried out using UV detection at 254nm. Sample collection was delayed for 12 minutes, then 12 fractions were collected at 2 minute intervals.

Fractions 9 and 10 were the most interesting. Fraction 9 contained 1.3% C_{26} alcohol. Fraction 10 contained 4.4% C_{26} alcohol.

Example 5

This Example demonstrates the use of supercritical fluid chromatography (in particular using supercritical CO_2) as another extraction technique, for implementation of the invention.

The extraction was carried out in a progressive stepwise manner through a series of pressures at constant temperature, collecting whatever material was extracted at each step. The operating conditions were set as follows.

Temperature: 85°C
Pressures: 80/100/120/140/160/200/250 bar
Time at each pressure: 30 mins
Collection method: Cooled open vial
System configuration: As shown in Figure 1 of the accompanying drawings
Cell configuration: As shown in Figure 2 of the accompanying drawings

The extraction cell was charged with 9.770g of lanolin alcohols (ARGOWAX distilled, batch no. WM 1757, Westbrook Lanolin Company) sealed and loaded into the extraction system (as illustrated in the drawings mentioned above). The oven was then switched on and allowed to equilibrate to 85°C for 20 mins in order to liquefy the lanolin. Once equilibrated, CO_2 was added at cylinder pressure (approximately 50 bar) and a further 5 minutes was allowed to elapse before the pressure was increased with the pump set in constant pressure (CP) mode to the starting pressure of 80 bar. The metering valve was then opened slowly until the desired CO_2 flow rate of approx 2.0mls/min was obtained. Once the flow had steadied the pump operating mode was changed to constant flow (CF) mode and set to 2.0mls/min. From this point the metering valve acts as a

back pressure regulator. This flow was maintained for a timed period of 30 mins.

The sample was collected in a pre-weighed open vial which was cooled using a dry ice bath. A loose plug of glass wool was placed into the top of the vial in order to prevent small particles being swept out by the escaping gaseous CO_2.

The pressure was then increased to the next set point and the extract collected for each pressure. The vials were then reweighed to determine the amount of material collected.

Owing to the fact that no solvent was used in the collection procedure, volatile materials may not have been trapped and so may have been lost.

Each of the isolated fractions was analysed as in Example 1. The results are set out in Table 4 below.

Table 4

Fraction	1a	2a	3a	4a	5a	6a	7a	8a	9a
P/Bar	80	100	120	140	160	200	250	De-comp	Residue
C20	nd	nd	nd	0.78	nd	0.47	1.76	0.79	0.57
C21	nd	nd	nd	0.11	nd	nd	0.17	nd	nd
C22	nd	nd	nd	0.43	0.52	nd	1.17	0.69	0.59
C23	nd	nd	nd	nd	nd	nd	nd	nd	nd
C24	nd	nd	nd	0.52	0.89	0.34	2.25	1.77	1.41
C25	nd	nd	nd	nd	nd	nd	nd	nd	nd

C26	nd	nd	nd	0.25	0.62	0.11	1.47	1.62	1.32
C27	nd	nd	nd	nd	nd	nd	nd	nd	nd
C28	nd	nd	nd	nd	nd	nd	nd	nd	nd
C30	nd	nd	nd	nd	nd	nd	nd	nd	nd
C32	nd	nd	nd	nd	nd	nd	nd	nd	nd
C35	nd	nd	nd	nd	nd	nd	nd	nd	nd

Supercritical extraction of lanolin alcohols (WM 1757) at 85°C at 250 kg cm^{-2} thus yielded a fraction containing 6.8% of alcohols in the range C_{20} to C_{26}. This is in good agreement with the teaching of published International Patent Application WO 94/07830, page 2, which states that supercritical CO_2, at temperatures in the range 25°C to 100°C and pressures between 60 and 300 kg cm^{-2}, have been used to extract 5% of alcohols in the range C_{20} to C_{36} from hydrolysed sugar cane wax.

Page 3, however, of this prior art reference states that molecular distillation is not an economical process. However, we have found that it may be so suitable for the application of the invention, as the following Example 6 demonstrates.

Example 6

This example demonstrates the use of molecular distillation (MD) (short path distillation) as the extraction technique. Anhydrous pharmaceutical lanolin (batch number LM 3160, P95, Westbrook Lanolin Company) was distilled in the laboratory on a GEA Canzler short-path

evaporator (model LK 50) at 200°C and 0.05 mBar pressure. Samples of lanolin before and after MD, and a sample of the distillate fraction, were collected and were analysed as in Example 1. The results are set out in Table 5 below.

Table 5

	Lanolin pre-MD	Lanolin-post-MD	Distillates
C20	nd	nd	nd
C21	nd	nd	nd
C22	nd	nd	0.85
C23	nd	nd	nd
C24	nd	nd	3.65
C25	nd	nd	nd
C26	0.18	nd	3.08
C27	nd	nd	nd
C28	nd	nd	1.19
C30	nd	nd	nd
C32	nd	nd	nd
C35	nd	nd	nd

This is a potentially effective way of obtaining a C_{20} to C_{28} rich fraction, which is particularly rich in C_{24} and C_{26} alcohols.

Example 7

This example demonstrates the making of lanolin alcohols from the three distilled lanolin fractions of Example 6 above. The same molecular distillation procedure

was carried out on each of those fractions and they were analysed as in Example 1.

The results are set out in Table 6 below.

Table 6

	From pre-MD	From-post-MD	From Distillates
unsaponifiables %w/w	48.80	47.80	48.72
unsaponifiables AV (acid value)	3.36	4.01	3.89
acids %	51.34	52.50	50.70
total %	100.14	101.41	99.42
C20	nd	nd	nd
C21	nd	nd	nd
C22	0.17	0.12	1.04
C23	nd	nd	nd
C24	0.40	nd	4.27
C25	nd	nd	nd
C26	0.28	0.10	3.24
C27	nd	nd	nd
C28	1.02	0.32	0.92
C30	nd	nd	nd
C32	nd	nd	nd
C35	nd	nd	nd

Lanolin alcohols obtained from hydrolysis of the distillate fraction yielded 9.47% of higher aliphatic alcohols in the range C_{22} to C_{28}.

Example 8

This example demonstrates the use of fractional solvent crystallisation as another technique for implementation of the present invention.

4, 5 and 10% w/w solutions of lanolin alcohols (ARGOWAX distilled, batch no. WM 1757) in warm 99% IMS (Industrial Methylated Spirit) were allowed to stand for 24 hours at room temperature. The precipitates were filtered and both layers evaporated to dryness and they were then analysed as in Example 1. The results are set out in Table 7 below.

Table 7

	4% ppt	4% soluble	5%ppt	5% soluble	10% ppt	10% soluble
C20	nd		nd	nd	nd	nd
C21	nd		nd	nd	nd	nd
C22	0.44		0.48	0.33	0.37	0.29
C23	nd		nd	nd	nd	nd
C24	4.53		5.12	0.74	0.92	0.48
C26	8.22		10.16	0.68	1.48	0.42
C27	nd		nd	nd	nd	nd
C28	4.72		5.46	?	0.45?	?
C30	1.88		2.09	nd	1.83?	nd
C32	nd		nd	nd	nd	nd
C35	nd		nd	nd	nd	nd

? = mixed peaks

CLAIMS

1. A method of extracting n-hexacosanol, either per se or as a n-hexacosanol-rich mixture of aliphatic alcohols, comprising extracting the alcohol or alcohol mixture from lanolin alcohols.

2. A method according to claim 1, wherein an n-hexacosanol-rich mixture of aliphatic alcohols is extracted which comprises n-hexacosanol in an amount of at least 2% by weight of a C_{20}-C_{32} fraction of the alcohol mixture.

3. A method according to claim 1, comprising a preliminary step of subjecting lanolin or wool wax to hydrolysis, and then extracting or concentrating the said alcohol or alcohol mixture from the resulting mixture of lanolin alcohols.

4. A method according to claim 3, wherein the lanolin or wool wax has previously been purified so as to be hypoallergenic.

5. A method according to any one of claims 1 to 4, further including the step of concentrating or isolating n-hexacosanol from the said extracted alcohol mixture.

6. A method according to claim 1 comprising a preliminary step of preparing the said lanolin alcohols from lanolin oil or lanolin esters.

7. A method according to any preceding claim, wherein the said aliphatic alcohol mixture is extracted from the lanolin alcohols by gel-permeation chromatography.

8. n-hexacosanol as or when produced by the method of any one of claims 1 to 7.

9. A n-hexacosanol-rich mixture of aliphatic alcohols as or when produced by the method of any one of claims 1 to 7.

10. A n-hexacosanol-rich mixture of aliphatic alcohols according to claim 9, comprising n-hexacosanol in an amount of at least 2%, by weight of a C_{20}-C_{32} aliphatic alcohol fraction of the alcohol mixture.

11. Use of lanolin, a lanolin derivative or lanolin alcohols as a source of n-hexacosanol.

12. A method of extracting n-hexacosanol, or an n-hexacosanol-rich mixture of aliphatic alcohols, or n-hexacosanol as or when produced thereby, or the use of lanolin, a lanolin derivative or lanolin alcohols, substantially as described herein.

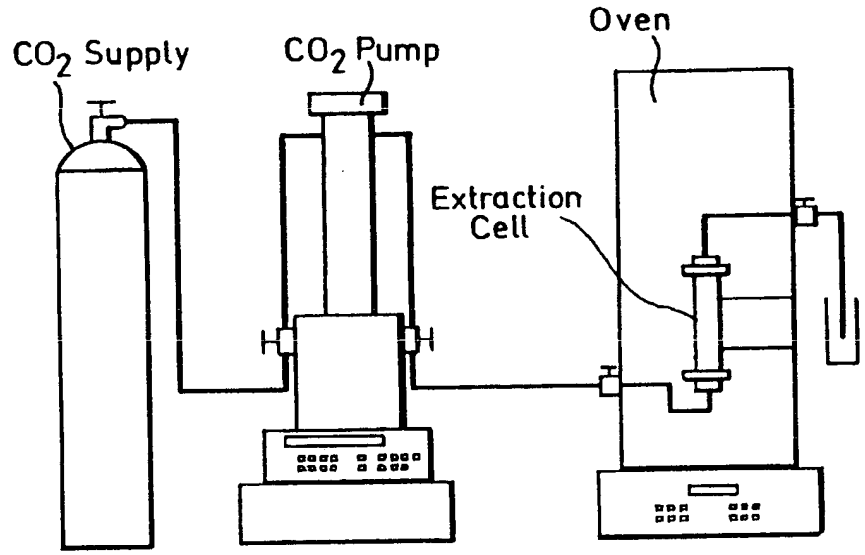
CO_2 Supply
CO_2 Pump
Oven
Extraction Cell

FIG.1.

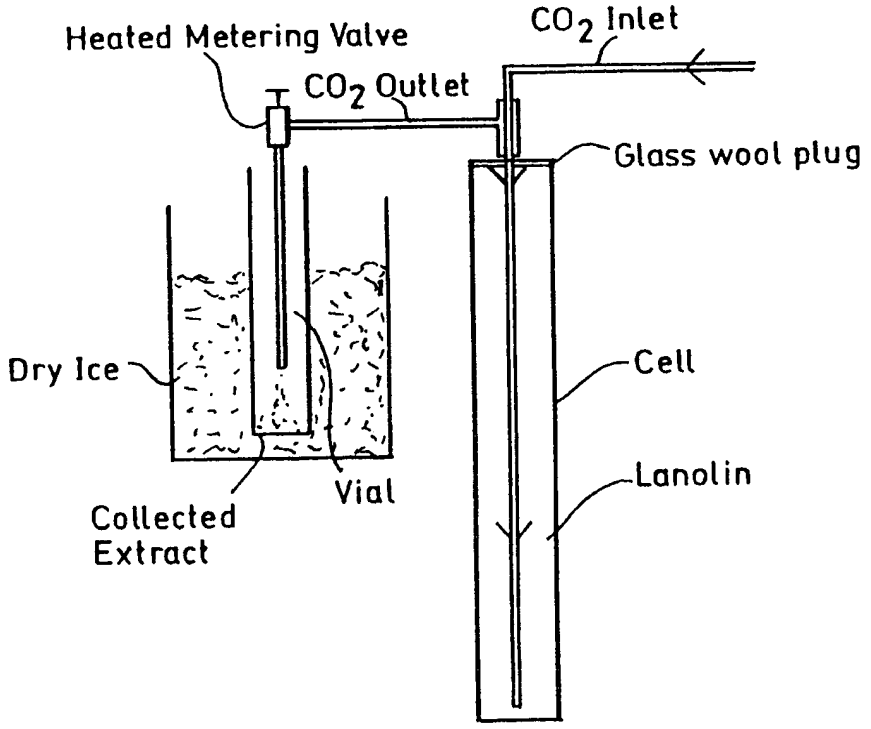
Heated Metering Valve
CO_2 Inlet
CO_2 Outlet
Glass wool plug
Dry Ice
Cell
Lanolin
Vial
Collected Extract

FIG.2.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 99/00879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C29/76 C07C29/88 C07C31/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REITER-REIMERS, MARIA ET AL: "The analysis of wool wax in cosmetics. I. Investigation of wool wax and modified wool waxes" Z. LEBENSM.-UNTERS. FORSCH. (1986), 183(3), 186-90 CODEN: ZLUFAR;ISSN: 0044-3026, XP002104359 see page 188 - page 189; figures 2,4 ---	1-11
Y	WO 94 07830 A (DALMER LAB SA ;ADANIFER SA (CH); LAGUNA GRANJA ABILIO (CU); MAGRAN) 14 April 1994 cited in the application see page 3 - page 4; claims 5-12 see page 5 - page 6; claims 1-4 ---	1-11
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 1999	17/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Arias-Sanz, J

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 99/00879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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